Chapter 3
Amino Acids and Peptides

SUMMARY

Section 3.1

- The amino acids that occur in proteins consist of an amino group and a carboxyl group bonded to the same carbon atom. The other two bonds of the carbon are to a hydrogen and to a side chain group, shown as R in diagrams.
- The amino acids found in proteins are not superimposable on their mirror images (with the exception of glycine). The mirror images known as L-amino acids are found in proteins, not the D-amino acid mirror image molecules.

Section 3.2

- Amino acids are classified according to two major criteria: the polarity of the side chains and the presence of an acidic or basic group in the side chain.
- There are four groups of amino acids found in proteins: first, those with nonpolar side chains; second, those with polar uncharged side chains; third, those with carboxyl groups in their side chains; fourth, those with basic side chains.

Section 3.3

- The carboxyl group of every amino acid is acidic, and the amino group is basic. The carboxylate group is the conjugate base of the carboxyl group, and the protonated amino group is the conjugate acid of the amino group. In addition, a number of side chains have groups with acid-base properties.
- Titration curves can be obtained for amino acids, just as they can for any diprotic or multiprotic acid. It is possible to determine the charge on amino acids at any given pH.

Section 3.4

- When the carboxyl group of one amino acid reacts with the amino group of another to give an amide linkage and eliminate water, a peptide bond is formed. In a protein, upward of a hundred amino acids are so joined to form a polypeptide chain.
- The peptide group is planar as a result of resonance stabilization. This stereochemical feature determines a number of features of the three-dimensional structure of proteins.

Section 3.5

- Small peptides play many roles in organisms. Some, such as oxytocin and vasopressin, are important hormones.

LECTURE NOTES

While students may have been introduced to amino acids in previous classes, such as organic chemistry, it is unlikely that they will know this material to any significant depth.

The structures and chemical natures of the twenty common amino acids is presented, following an introduction reminding students of stereochemistry concepts. This is followed by a discussion of the acid and base properties of amino acids. The chapter concludes with an introduction to the nature of the peptide bond, and a brief survey of some small physiologically important peptides. Most students do have a difficult time picturing three-dimensional objects, so the use of molecular models is recommended.

This chapter can be expected to require at least two lectures. The first devoted to the general structure of the amino acids, and the second to their titration curves. The material peptide bonds and small peptides may involve a third lecture.

LECTURE OUTLINE

I. Amino Acid Structure
    A. Stereochemistry
        1. Chirality
        2. D and L stereoisomers
    B. Survey of individual amino acids
        1. Nonpolar side chains
        2. Neutral polar side chains
        3. Acidic side chains
        4. Basic side chains
        5. Uncommon amino acids
II. Acid/Base properties
    A. Independent ionization of carboxyl, amino, and side chain groups
    B. Charge dependence on pH
        1. Zwitterions
        2. Electrophoresis
        3. Isoelectric pH
III. Peptide bonds
    A. Formation
    B. Planar nature of bond
IV. Small peptides of biological interest

ANSWERS TO PROBLEMS

3.1 Amino Acids Exist in a Three-Dimensional World

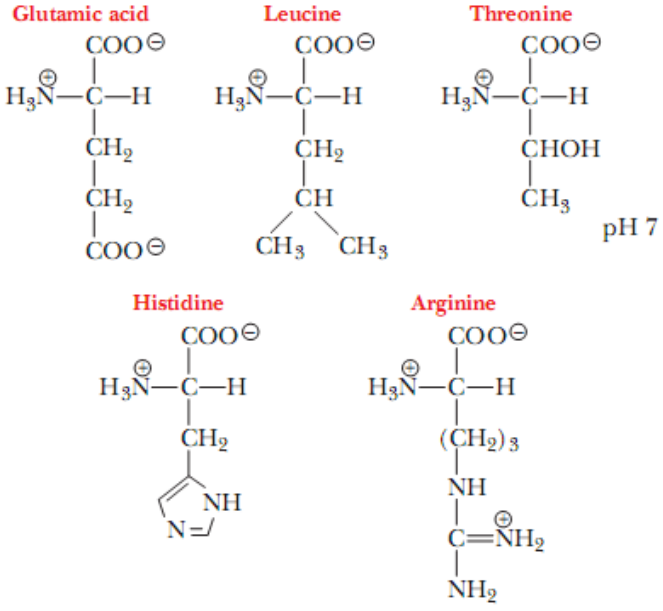
1. D- and L-amino acids have different stereochemistry around the α-carbon. Peptides that contain D-amino acids are found in bacterial cell walls and in some antibiotics.

3.2 Individual Amino Acids: Their Structures and Properties

2. Proline is technically not an amino acid. Glycine contains no chiral carbon atoms.
3. Listed here are amino acids in which the R group contains the following: a hydroxyl group (serine, threonine, or tyrosine); a sulfur atom (cysteine or methionine); a second chiral carbon atom (isoleucine or threonine); an amino group (lysine); an amide group (asparagine or glutamine); an acid group (aspartate or glutamate); an aromatic ring (phenylalanine, tyrosine, or tryptophan); a branched side chain (leucine or valine).
4. In the peptide Val—Met—Ser—Ile—Phe—Arg—Cys—Tyr—Leu, the polar amino acids are Ser, Arg, Cys, and Tyr; the aromatic amino acids are Phe and Tyr; and the sulfur-containing amino acids are Met and Cys.
5. In the peptide Glu—Thr—Val—Asp—Ile—Ser—Ala, the nonpolar amino acids are Val, Ile, and Ala; the acidic amino acids are Glu and Asp.
6. Amino acids other than the usual 20 are produced by modification of one of the common amino acids. See Figure 3.5 for the structures of some modified amino acids. Hydroxyproline and hydroxylysine are found in collagen; thyroxine is found in thyroglobulin.

3.3 Amino Acids Can Act as Both Acids and Bases

7. The ionized forms of each of the following amino acids at pH 7—glutamic acid, leucine, threonine, histidine, and arginine—are as follows:



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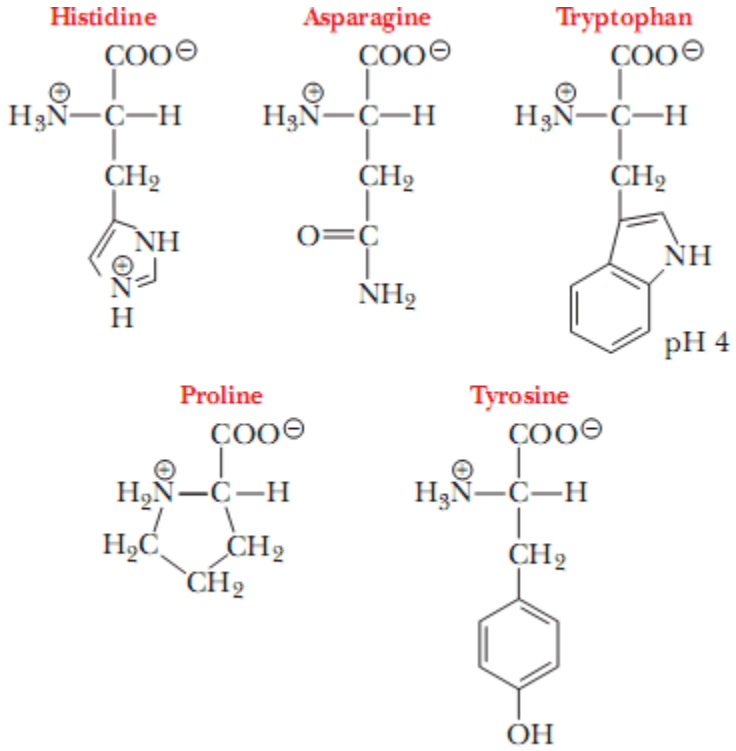
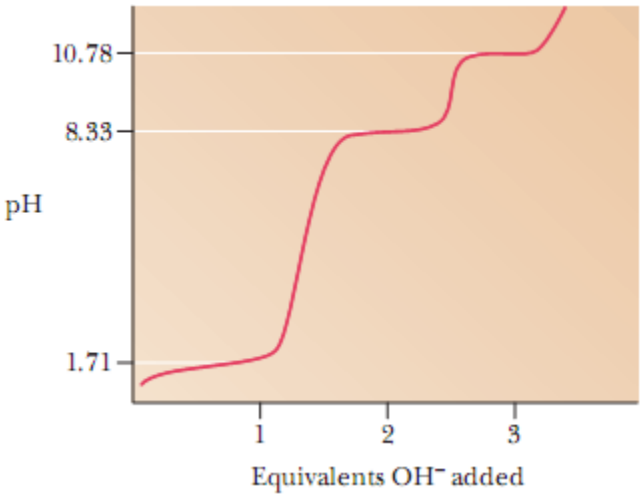


9. Histidine: imidazole is deprotonated, α-amino group is predominantly deprotonated. Asparagine: α-amino group is deprotonated. Tryptophan: α-amino group is predominantly deprotonated. Proline: α-amino group is partially deprotonated. Tyrosine: α-amino group is predominantly deprotonated, phenolic hydroxyl is approximately a 50–50 mixture of protonated and deprotonated forms.

10. Glutamic acid, 3.25; serine, 5.7; histidine, 7.58; lysine, 9.75; tyrosine, 5.65; arginine, 10.75.

11. Cysteine has no net charge at pH 5.02 = (1.71 + 8.33)/2 (see titration curve below).



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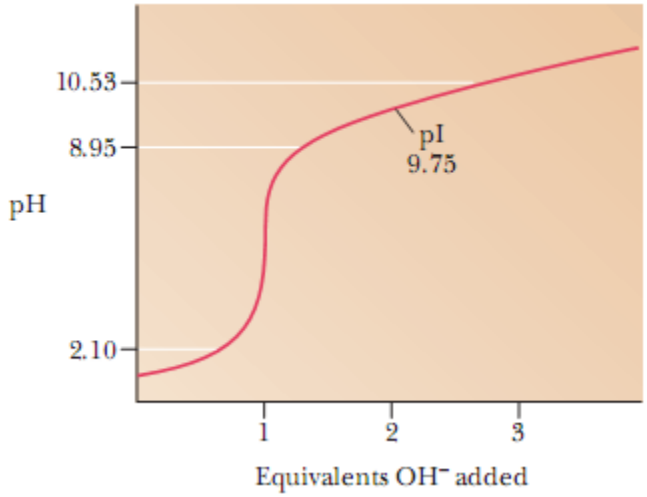
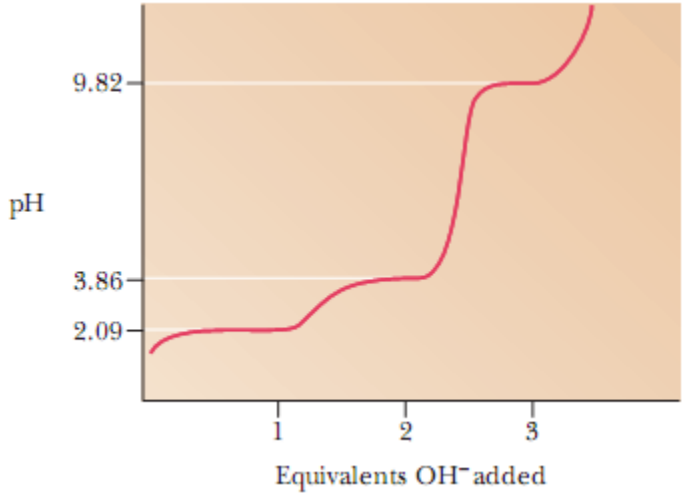


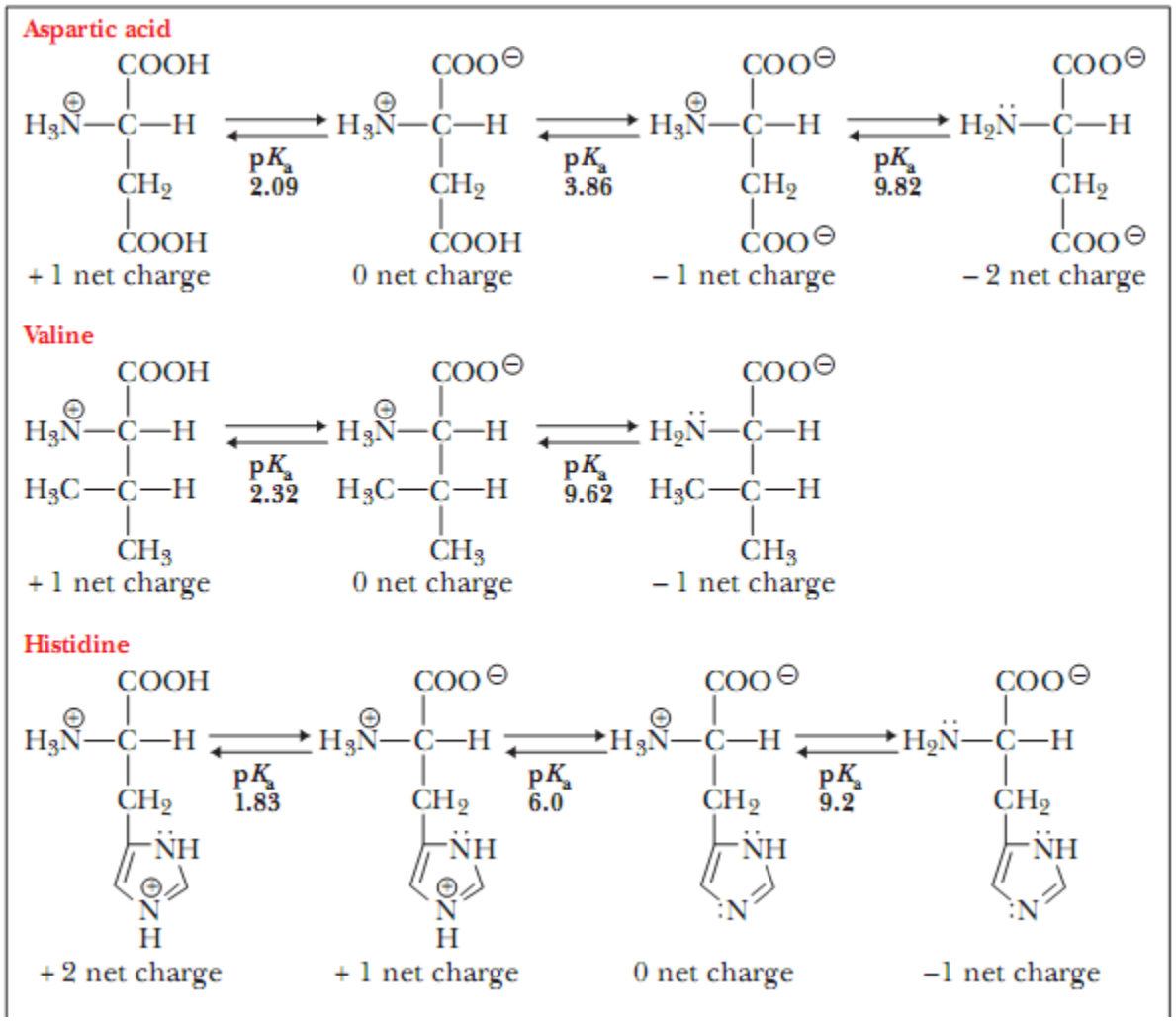
13. In all cases, the yield is 0.95^n. For 10 residues, that means 60% yield; for 50 residues, 8%; and for 100 residues, 0.6%. These are not satisfactory yields. Enzyme specificity gets around the problem.

14. The conjugate acid–base pair acts as a buffer in the pH range 1.09–3.09.



15. They have a net charge at pH extremes, and the molecules tend to repel each other. When the molecular charge is zero, the amino acids can aggregate more easily.

16. The ionic dissociation reactions of the amino acids aspartic acid, valine, histidine, serine, and lysine are as follows:



17. The pK_a for the ionization of the thiol group of cysteine is 8.33, so this amino acid could serve as a buffer in the —SH and S^{2-} forms over the pH range 7.33–9.33. The α-amino groups of asparagine and lysine have pK_a values of 8.80 and 8.95, respectively; these are also possible buffers, but they are both near the end of their buffer ranges.
18. At pH 4, the α-carboxyl group is deprotonated to a carboxylate, the side-chain carboxyl is still more than 50% protonated, and both amino groups are protonated. At pH 7, both the α-carboxyl group and the side-chain carboxyl group are deprotonated to a carboxylate, and both amino groups are protonated. At pH 10, both the α-carboxyl group and the side-chain carboxyl group are deprotonated to a carboxylate, one of the amino groups is primarily deprotonated, and the other amino group is a mixture of the protonated and deprotonated forms.
19. The pI refers to the form in which both carboxyl groups are deprotonated, and both amino groups protonated at pH 6.96.
20. At pH 1, the charged groups are the N-terminal NH_3^+ on valine and the protonated guanidino group on arginine, giving a net charge of +2. The charged groups at pH 7 are the same as those at pH 1, with the addition of the carboxylate group on the C-terminal leucine, giving a net charge of +1.
21. Both peptides, Phe—Glu—Ser—Met and Val—Trp—Cys—Leu, have a charge of +1 at pH 1 because of the protonated N-terminal amino group. At pH 7, the peptide on the right has no net charge because of the protonated N-terminal amino group and the ionized C-terminal carboxylate negative charge. The peptide on the left has a net charge of –1 at pH 7 because of the side-chain carboxylate group on the glutamate in addition to the charges on the N-terminal and C-terminal groups.
22.

(a) Lysine, because of the side-chain amino group.
(b) Serine, because of the lack of a side-chain carboxyl.

23. Glycine is frequently used as the basis of a buffer in the acid range near the pK of its carboxyl group. The useful buffer range is pH 1.3–3.3.

3.4 The Peptide Bond

24. See Figure 3.10.
25. The resonance structures contribute to the planar arrangement by giving the CON bond partial double-bond character.
26. The peptide group would still be planar because the atoms that form the bond are the same.
27. The free carboxyl group and the free amino group of a peptide are both titratable and could serve as a buffer. The same is true for any titratable groups on the side chains. It would not necessarily be a particularly effective buffer.
28. The two peptides differ in amino acid sequence but not in composition.

29. The titration curves of the two peptides have the same general shape. The pK_a values of the α-amino and α-carboxyl groups differ. Very careful work will show slight differences in side-chain pK_a values because of the different distances to the charged groups at the ends of the peptide. Such changes are particularly marked in proteins.
30. Asp—Leu—Phe; Leu—Asp—Phe; Phe—Asp—Leu; Asp—Phe—Leu; Leu—Phe—Asp; Phe—Leu—Asp
31. DLF; LDF; FDL; DFL; LFD; FLD
32. You would get $20^{100} \approx$ f1.27 × 10^{130} molecules, which is about 10^{84} Earth volumes. The same calculation for a pentapeptide gives more comprehensible results.
33. There are two possible products, alanyl glycine (free amino group on alanine, free carboxyl on glycine), and glycyl alanine (free amino group on glycine, free carboxyl group on alanine).
34. Side chains are not directly bonded to any of the atoms of the peptide bond.
35. Side chains do not enter into the peptide bond themselves, but large groups with chiral centers could sterically hinder bond formation.
36. They are relatively stable because they are zwitterions. They typically have high melting points.
37. With very little doubt, no. Compare predicting the properties of water from those of hydrogen and oxygen, in either atomic or molecular form. If you knew the properties of the protein, you might be able to do the reverse to some extent.
38. The amino acids thyroxine and hydroxyproline occur in very few proteins. The genetic code does not include them, so they are produced by modification of tyrosine and proline, respectively.
39. These two peptides differ chemically. The open chain has a free C-terminal and N-terminal, but the cyclic peptide has only peptide bonds.
40. Both the C-terminal and the N-terminal of the open-chain peptide can be charged at appropriate pH values, which is not the case with the cyclic peptide. This can provide a basis for separation by electrophoresis.
41. Carbohydrates are not a source of the nitrogen needed for biosynthesis of amino acids.
42. Suggest that your friend shows the carboxyl group as a charged carboxylate (—COO^-) and the amino group in its charged form (—NH_3^+).
43. Very few side chains have functional groups to form crosslinks.
44. Many more conformations would be possible because of free rotation around the peptide bond.
45. There would be no possibility of disulfide crosslinks within or between peptide chains, giving more possible conformations. There would not be the possibility of oxidation–reduction reactions involving sulfhydryl and disulfide groups.
46. The big difference would be the loss of stereospecificity in the conformation of any peptide or protein. This would have drastic consequences for the kinds of reactions of the protein.

3.5 Small Peptides with Physiological Activity

47. Oxytocin has an isoleucine at position 3 and a leucine at position 8; it stimulates smooth muscle contraction in the uterus during labor and in the mammary glands during lactation. Vasopressin has a phenylalanine at position 3 and an arginine at position 8; it stimulates resorption of water by the kidneys, thus raising blood pressure.
48. Oxytocin stimulates smooth muscle contraction in the uterus during labor and in the mammary glands during lactation. Vasopressin stimulates resorption of water by the kidneys, thus raising blood pressure.
49. The disulfide bond is responsible for the cyclic structure of both oxytocin and vasopressin.
50. Peptide bonds double back on themselves to form a cyclic structure.